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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/582,184	09/26/2007	Samir Bennabi	BHC 031069	8960

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EXAMINER	
O DELL, DAVID K	

ART UNIT	PAPER NUMBER
1625	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,184	BENNABI ET AL.	
	Examiner	Art Unit	
	DAVID K. O DELL	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-14* is/are pending in the application.

4a) Of the above claim(s) *4,6-9,12 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,10,11 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This application is a 371 of PCT/EP04/13430 filed 11/26/2004, which claims priority to GERMANY 103 57 510.3 filed 12/09/2003.

Claims 1-4, 6-14 are pending.

Claim Rejections/Objections Withdrawn

2. The rejection of claims 1-3, 5, 10 under 112 1st paragraph is withdrawn based on the amendments to the claims. The rejection of claims 1-3, 5, 10 under 35 U.S.C. 102(e) as being anticipated by Borzilleri et. al. US PGPub 20060004006 A1 is withdrawn. The applicant's representative has challenged the validity of the document as prior art under 102(e). The document is available as prior art under 35 U.S.C. 102(e) as of the effective U.S. filing dates. See MPEP § 706.02(f)(1) for a discussion of what constitutes a U.S. filing date. In this case the provisional application US 2004-612563P filed 20040923 provides support in the manner prescribed by 112 1st paragraph for the species 134 and 135. The rejection was therefore proper. However such consideration is irrelevant since the claims have been amended to exclude these species. The US PGPub 20060004006 A1 fails to describe generically the A moieties required for the instant claims (although such a genus is described in the priority document US 2004-612563P). A CIP of this case (US 20060211695 A1) claiming priority to the material described in US 2004-612563P does describe the genus. This document, also prior art under 102(e), now forms the basis of a 103(a) rejection.

The objection to claims 11-12 under 37 CFR 1.75(c) as being in improper form is withdrawn.

Claim Rejections/Objections Maintained/ New Grounds of Rejection

3. The US PGPub 20060211695 A1 claiming priority to the material described in US 2004-612563P 20040923 (102(e) date) now forms the basis of a 103(a) rejection. A new rejection of claims 11 and 13 is now made based on the amended claims under 112 1st paragraph. As detailed in the following rejections, the generic claim encompassing the elected species was not found patentable. Therefore, the provisional election of species is given effect, the examination is restricted to the elected species only, and claims not reading on the elected species are held withdrawn. Accordingly claims 12, 14 are withdrawn as not reading on the elected species of intended use "hypertension". Claims 4, 6-8 are withdrawn as being drawn to a non-elected invention,

Claim Rejections – 35 USC § 103

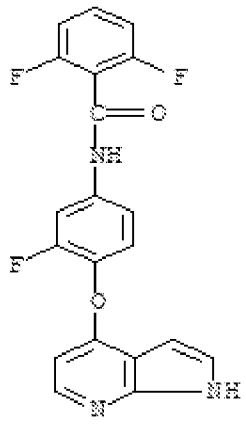
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-3, 10, 11, 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Borzilleri et. al. US PGPub 20060211695 A1 (priority to US 2004-612563P 20040923 (102(e) date)). The factual inquiries set forth in Graham **v.** John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

Determination of the scope and content of the prior art (MPEP 2141.01)

Borzilleri et. al. document teaches species that are nearly anticipatory including:



In addition the genus of claim 12 where "A" is the same describes compounds at least where instant R6 is phenyl. This R6 moiety is described as R4 in Borzilleri. Claim 5 lists preferred embodiments as "optionally substituted phenyl" and pyrollidinyl. According to paragraph [0036]:

> **[0036]** In some embodiments of the present invention, R^4 is an optionally substituted phenyl, an optionally substituted pyridyl, an optionally substituted pyrrolidinyl, an optionally substituted pyridyl-N-oxy, or an optionally substituted pyridinonyl or pyrimidinonlyl, wherein said substituent is selected, for example, from hydroxyl, halo, C_1 to C_4alkyl, C_3 to C_7 cycloalkyl, CN, alkylthio, alkoxy, phenyl, amino, heterocycloalkyl, aminoalkylamino and alkylaminoalkoxy. In some embodiments of the present invention, the substituent is F, Br, Cl, methyl, pentyl, methoxy, phenyl, morpholinyl, NH_2, or $NHCHNH_2$.

Ascertainment of the difference between the prior art and the claims

It is clear that the prior art differs only in a failure to actually exemplify all of the possible optional substituents on the R6 phenyl in a single compound. Many were exemplified, including

some of the instant claims where prior art A was a different fused pyridine. At least the unsubstituted compound is described and the alkyl overlaps with the instant claims.

> where phenyl or thienyl ~~aryl or heteroaryl~~ may be substituted by ~~amino, hydroxyl, halogen, cyano,~~ (C_1-C_6)-alkyl[[,]] which for its part may be substituted by amino or (C_1-C_6)-alkylamino, ~~(C_1-C_6)-alkoxy, (C_1-C_6)-alkylamino or (C_1-C_6)-alkoxycarbonyl~~,

The alkylamino differs from the prior art amino by (CH_2). Some of the claims recite intended use. Intended use has no bearing on a composition of matter claim unless the use imparts a structural change, which in the instant case it does not.

Finding of prima facie obviousness

Rational and Motivation
(MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use further species of the compounds of those of Borzilleri et. al. to produce the instant invention. The compounds are described as shown above. In addition at least for the instantly claimed embodiment where the C1 alkyl is an optional substituent the difference from the prior art compound without the substituent is H to Me. The interchangeability of hydrogen and methyl generally creates a case of prima facie obviousness. See In Re Herr 134 USPQ 176 (C.C.P.A. 1962), finding the presence of a methyl group failing to create a patentable distinction over the prior art ("The only structural distinction in appellant's compounds over those of Herr et al. is the presence of a methyl group in the 17 position of the claimed compounds. It is noted that

the two compounds used as standards in the art have exactly the same structural difference. It therefore appears, as the board held, that the 17-methyl derivative of Herr et al. would be an obvious structural change to a chemist of ordinary skill in that field.") See also In re Wood, Whittaker, Stirling, and Ohta, 199 USPQ 137 (C.C.P.A. 1978) and In re Lahr, 137 USPQ 548, 549 (C.C.P.A. 1963). Also discussed as an ancillary issue in In Re Paquette 165 USPQ 317, "we also think it would be obvious to the person skilled in the art to provide dimers of an N-methyl-2-pyridone modified by the presence of a methyl substituent on one of the otherwise unsubstituted carbons of the ring. Since little could be more expected than that the resulting dimer would have two such substituents, that fact clearly does not detract from the obviousness of claims 15-18."

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (In re Opprecht 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); In re Bode 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 11 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The claims are extremely broad encompassing an unknown list of diseases, described only as "cardiovascular disorders" a partial list of disorders in the specification includes: "such as, for example, hypertension and cardiac insufficiency, stable and unstable angina pectoris, disorders of peripheral and cardiac vessels, of arrhythmias, of thrombolic disorders and ischaemias, such as myocardial infarction, stroke, transitory and ischaemic attacks, obstruction of peripheral circulation, subarachnoidal haemorrhages, prevention of restenoses, such as, for example, after

thrombolysis therapies, percutaneous transluminal angioplasties (PTA), percutaneous transluminal coronary angioplasties (PTCA), bypass," other such "cardiovascular disorders" include acute coronary syndrome, acute idiopathic pericarditis, acute rheumatic fever, American trypanosomiasis (Chagas' disease), angina pectoris, ankylosing spondylitis, anomalous pulmonary venous connection, anomalous pulmonary venous drainage, aortic atresia, aortic regurgitation, aortic stenosis, aortic valve insufficiency, aortopulmonary septal defect, asymmetric septal hypertrophy, asystole, atrial fibrillation, atrial flutter, atrial septal defect, atrioventricular septal defect, autoimmune myocarditis, bacterial endocarditis, calcific aortic stenosis, calcification of the cental valve, calcification of the valve ring, carcinoid heart disease, cardiac amyloidosis, cardiac arrhythmia, cardiac failure, cardiac myxoma, cardiac rejection, cardiac tamponade, cardiogenic shock, cardiomyopathy of pregnancy, chronic adhesive pericarditis, chronic constrictive pericarditis, chronic left ventricular failure, coarctation of the aorta, complete heart block, complete transposition of the great vessels, congenital bicuspid aortic valves, congenital narrowing of the left ventricular outflow tract, congenital pulmonary valve stenosis, congenitally corrected transposition of the great arteries, congestive heart failure, constrictive pericarditis, cor pulmonale, coronary artery origin from pulmonary artery, coronary atherosclerosis, dilated (congestive) cardiomyopathy, diphtheria, double inlet left ventricle, double outlet right ventricle, Ebstein's malformation, endocardial fibroelastosis, endocarditis, endomyocardial fibrosis, eosinophilic endomyocardial disease (Loffler endocarditis), fibroma, glycogen storage diseases, hemochromatosis, hypertensive heart disease, hyperthyroid heart disease, hypertrophic cardiomyopathy, hypothyroid heart disease, idiopathic dilated cardiomyopathy, idiopathic myocarditis, infectious myocarditis, infective endocarditis, ischemic

heart disease, left ventricular failure, Libman-Sachs endocarditis, lupus erythematosus, lyme disease, marantic endocarditis, metastatic tumors, mitral insufficiency, mitral regurgitation, mitral stenosis, mitral valve prolapse, mucopolysaccharidoses, multifocal atrial tachycardia, myocardial ischemia, myocardial rupture, myocarditis, myxomatuos degeneration, nonatheromatous coronary artery disease, nonbacterial thrombotic endocarditis, noninfectious acute pericarditis, nonviral infectious pericarditis, oblitaerative cardiomyopathy, patent ductus arteriosus, pericardial effusion, pericardial tumors, pericarditis, persistent truncus arteriosis, premature ventricular contraction, progressive infarction, pulmonary atresia with intact ventricular septum, pulmonary atresia with vertricular septal defect, pulmonary insufficiency, pulmonary regurgitation, pulmonary stenosis, pulmonary valve lesions, pulmonary valve stenosis, pyogenic pericarditis, Q fever, radiations myocarditis, restrictive cardiomyopathy, rhabdomyoma, rheumatic aortic stenosis, rheumatic heart disease, rocky mountain spotted fever, rupture of the aortic valve, sarcoid myocarditis, scleroderma, shingolipidoses, sinus brachycardia, sudden death, syphilis, systemic embolism from mural thrombi, systemic lupus erythematosus, tetralogy of fallot, thiamine deficiency (Beriberi) heart disease, thoracic outlet syndrome, Torsade de Pointes, toxic cardiomyopathy, toxic myocarditis, toxoplasmosis, trichinosis, tricuspid atresia, tricuspid insufficiency, tricuspid regurgitation, tricuspid stenosis, tricuspid valve lesions, tuberculuos pericarditis, typhus, ventricular aneurysm, ventricular fibrillation, ventricular septal defect, ventricular tachycardia, ventriculoarterial septal defect, viral pericarditis, and Wolff-Parkinson-White syndrome. Thus, the scope is broad. The elected intended use is hypertension.

(B) This is a compound invention but it requires the use of the intended use of prophylaxis and treatment of diseases and disorders. This claim is ostensibly being evaluated as a method claim.

(D) One of ordinary skill is a medical doctor.

(C) (E) The existence of a "silver bullet" for all these cardiovascular diseases is contrary to our present understanding of pharmacology and medicine. According to Fukata et. al. "Rho–Rho-kinase pathway in smooth muscle contraction and cytoskeletal reorganization of non-muscle cells" TRENDS in Pharmacological Sciences Vol. 22 No.1 January 2001, pgs. 32-39 (cited on the IDS) interest in Rho kinase inhibition is related to cardiovascular disorders, however the authors come to the conclusion that "Although much progress has been made, the following questions remain to be answered. First, how is the activity of the Rho–Rho-kinase pathway regulated downstream of various extracellular signals? It could involve much crosstalk with other members of Rho family GTP-binding proteins, Rac and Cdc42, and their effectors. Second, how is the Rho–Rho-kinase pathway affected in the diseases mentioned above? Third, are the disorders of the Rho–Rho-kinase pathway as observed in animal models applicable to human patients? The answers to these questions will define the physiological and pathological roles of the Rho–Rho-kinase pathway more precisely and, in doing so, help develop effective therapies for diseases caused by hypercontraction of muscle."

The instant claims embrace all cardiovascular diseases with distinct etiologies and different treatments. There is not even a basic causal link between many of the diseases listed and the pathway claimed. In the field of Rho kinase inhibitors any therapeutic utility is speculative at this stage and only for a very limited set of diseases.

(F) In the instant case we have been given very limited information as to what these compounds are doing in the pharmacological sense. The only information in the specification is a reference to performance in a test tube assay for inhibiting a Rho kinase enzyme, pg. 76.

(G) The application has provided no working examples of the treatment of any disease. The clinical benefit of any Rho kinase inhibitor in the diseases mentioned above has never been demonstrated.

(H) Presumably to use this invention one would need to make all the compounds of claim 1 and test them against all the various diseases in animals or humans. It is not at all clear what these compounds would do inside an organism. Based on the teaching of Fukata the complexity of Rho kinase signaling precludes conclusions based solely on enzyme inhibition alone. It is clear that one could not use this invention that has no working examples in this unpredictable art without undue experimentation.

Conclusion

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DAVID K. O DELL whose telephone number is (571)272-9071. The examiner can normally be reached on Monday-Friday 9:00 A.M. to 6:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JANET ANDRES can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David K. O'Dell/
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